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Multiple myeloma among Blacks and Whites in the United States: the role of chronic antigenic stimulation

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Multiple myeloma (MM) is twice as common among Blacks than Whites in the United States. The reasons for this racial disparity are unknown, and the etiology of this cancer, in general, is poorly understood. Repeated or chronic antigenic stimulation (CAS) of the immune system has been suggested as a risk factor. Previous case-control studies have reported inconsistent CAS associations based on evaluations of individual and biologic categories of medical conditions. Interview data from 573 cases and 2,131 population-based controls were used to investigate further the CAS hypothesis using an immunologically based approach, and to determine whether CAS accounts for the excess of myeloma among Blacks. Over 50 medical conditions were grouped into biologically and immunologically related categories, and B-cell- and T-cell-mediated response groups. Except for urinary tract infections among Black men (odds ratio [OR] = 2.0), no significantly increased risks of MM were observed. However, there was a suggestion of increased risk among Blacks with an increased exposure to anaphylactic conditions. Analysis by immunoglobulin type revealed significantly elevated risks of IgG myeloma with eczema (OR = 2.1), the biologic category 'allergic conditions' (OR = 1.6), and the immunologic category 'anaphylaxis response' (OR = 1.6) among Whites, with Blacks having slightly lower risks. Our findings do not support a causal relationship between CAS and MM, nor do they explain the higher incidence among Blacks. *Cancer Causes and Control* 1994, 5, 529 - 539

Key words: Antigenic stimulation, case-control study, etiology, multiple myeloma, race, United States.

Introduction

In the United States, multiple myeloma (MM) is twice as common among Blacks than Whites.[1] The reason for this racial disparity is unknown, and the etiology of this neoplasm, in general, is poorly understood. On the

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basis of animal experimentation[2-5] and case reports,[6-11] it has been suggested that repeated or chronic antigenic stimulation (CAS) of the immune system may play a role in the development of MM. Although a number of case-control studies[12-23] have attempted to address the CAS hypothesis by evaluating MM risk associated with individual immune-stimulating medical conditions and biologic categories of such conditions, there have been few consistent findings.

To investigate the CAS hypothesis in more depth and to determine whether CAS may explain the two-fold excess of MM among Blacks, data were analyzed from a multicenter, population-based, case-control study designed to examine differences in risk factors for MM between Blacks and Whites. This paper presents the risks for MM and immunoglobulin subtypes associated with CAS using an approach that classifies the medical conditions by their respective underlying immune response mechanism. To evaluate whether CAS measured by this approach could explain the racial differences in incidence of this cancer, race-specific risks also are presented.

Materials and methods

A population-based, case-control, interview study of four cancer types that occur more commonly among Blacks than Whites (*i.e.*, MM, esophagus, pancreas, and prostate) was conducted during 1986-89 in three areas of the US. For efficiency, one general-population control-group was selected for all four cancer-types under investigation.

Selected for study were all MM cases newly diagnosed between 1 August 1986 and 30 April 1989 among White and Black men and women aged 30 to 79 years, who resided in one of three areas covered by population-based cancer registries. These included: the Georgia Center for Cancer Statistics (DeKalb and Fulton counties); the Metropolitan Detroit Cancer Surveillance System (Macomb, Oakland, and Wayne counties, Michigan) and the New Jersey State Cancer Registry (10 counties). Subjects were identified from hospital pathology, hematology, outpatient, and tumor registry records. Because of the poor prognosis of this cancer, a rapid-reporting system was developed to encourage the identification and interview of cases within three months of diagnosis. Immunoglobulin type of MM was determined from immunoelectrophoresis reports.

For control selection, a sampling frame was constructed using incidence data for the four types of cancer combined from previous years in each of the study areas to estimate the expected race, gender, and age distribution of the cases. Based on these estimates, population controls less than 65 years of age were selected at periodic intervals by random digit dialing (RDD), using a two-step process involving identification of households with eligible members for study and selection of potential controls to be contacted.[24] Prior to selection of controls, each household was assigned randomly as either male or female, and usually only one person was selected from each household. However, due to a deficit of numbers in some age/race/gender groups, it was necessary to select either both a male or female, or two subjects from a single household for 68 households. Computerized files of Medicare recipients provided by the Health Care Financing Administration (HCFA) stratified by age (65-69, 70-74, 75-79), gender, and race for each geographic area were used to systematically select (after a random start) population controls aged 65 to 79 years.

Cases and controls were interviewed in person by a trained interviewer, typically in the home setting. The questionnaire was designed to obtain detailed information on previous medical disorders, history of allergic conditions, sociodemographic factors, alcohol and tobacco use, dietary factors, and lifetime occupational history.

To assess the CAS hypothesis, medical conditions were grouped into biologic and immunologic categories. Five biologically related categories were created after review of over 50 medical conditions and include: childhood viral illnesses and vaccinations; acute bacterial infections; chronic bacterial infections; allergic conditions; and autoimmune diseases (Appendix). Individuals were assigned a 'yes' code for a specific biologically related category if they reported being diagnosed with any condition within the category. Each subject also was assigned a score for each biologically related category which corresponded to the number of conditions and the number of times that the individual had the condition. Some questions required that the individual had to have been diagnosed with a certain condition (*e.g.*, ear infection, strep throat) at least three times over the person's lifetime to qualify as having an immune-stimulating condition. Thus, the score count for these conditions began at three.

After consultation with several immunologists, seven distinct immunologically related categories were constructed (Appendix). The following five immunologic response categories had sufficient numbers to be included in the analysis: anaphylaxis; delayed-hypersensitivity; neutralization; neutralization and other responses; and neutralization and cytotoxicity. To assess whether the type of lymphocyte mediation influenced myeloma risk, conditions were grouped into two categories according to whether they were mediated primarily by B-cell immune response or

T-cell (*i.e.*, conditions with delayed-hypersensitivity response and conditions with granulomas) immune response (Appendix). Each individual also received a score for each immunologically related category which corresponded to the number of conditions and the number of times that the individual had the condition. Rheumatoid arthritis was dropped from the grouped analysis, as the reported prevalence among controls was considerably higher than in previous studies of national data,[25] suggesting possible over-reporting of this condition and perhaps confusion with other forms of arthritis. Conditions for which no appropriate biologic or immunologic category could be designated were omitted from that phase of the analysis.

Unconditional logistic regression was used to obtain maximum likelihood estimates of adjusted odds ratios (OR) and 95 percent confidence intervals (CI) using the BMDPLR procedure.[25] Race-specific ORs were adjusted for: gender; study site (Atlanta, Detroit, New Jersey); educational status (less than high school, high school, more than high school); and age (≤ 64, ≥ 65). Further stratification by four age groups did not alter substantially the risk estimates. Scores for the biologic and immunologic categories were subdivided into levels based on the distribution of the scores within the control group for the particular category of interest. To test for linear trend, the median value for controls within each level of exposure for a particular biologic or immunologic category was entered as a continuous variable in the logistic models. Both race-adjusted and race-specific risk estimates are presented in the tables. Race-gender-specific ORs also were calculated and, where significant, are included in the text. Interaction between race and certain immune-response categories was assessed by comparing the difference between the log-likelihoods of the logistic models containing the interaction term and models without the interaction term.

Results

Of the 581 White and 309 Black cases eligible for study, interviews were conducted with 367 (63.2 percent) White cases (193 males, 174 females) and 208 (67.3 percent) Black cases (92 males and 116 females). Reasons for nonresponse include: deceased prior to scheduling an interview (Whites 20.7 percent, Blacks 20.7 percent); refused to be interviewed (Whites 5.7 percent, Blacks 3.6 percent); physician refusal (Whites 2.9 percent, Blacks 1.3 percent); patient too ill (Whites 7.4 percent, Blacks 6.1 percent), and language or other problems (Whites 0.2 percent, Blacks 1.0 percent). One Black male and one Black female were excluded subsequently from the study due to unreliable questionnaire responses as assessed by the interviewer. Thus, the total number of cases used in the analysis of individual medical conditions was 367 Whites and 206 Blacks. For the analysis of categorized biologically and immunologically related conditions, only subjects with complete medical history and allergy sections of the questionnaire or who were missing less than five percent of these sections were included. The result of this subselection yielded 1,441 Whites (349 cases and 1,092 controls) and 1,110 Blacks (196 cases and 914 controls).

For the RDD controls, interview response rates were 78 percent for both Whites and Blacks. When accounting for the response rate (86 percent) to the initial phase of screening for eligibility among RDD contacts, the adjusted response rates were 67 percent for both races. The interview response rates for the HCFA controls were 73 percent for Whites and 78 percent for Blacks. Reasons for interview nonresponse among all controls included refusal (Whites, 17 percent; Blacks, 13 percent), deceased or too ill for interview (Whites, three percent; Blacks, five percent), and language and other problems (Whites, three percent; Blacks, four percent). Because there were no White cases in the 30 to 34 year age-group, 15 White controls in this age group (eight males and seven females) were omitted from further analysis. The total number of controls used in the analysis was 1,164 Whites (742 males and 422 females) and 967 Blacks (614 males and 353 females).

Distributions of the demographic characteristics of the cases and controls by race are presented in Table 1. The mean age of the White cases (65.3 years) was slightly greater than that of the Black cases (62.3 years). White cases and controls had more years of education and had higher incomes than Black cases and controls. Over 30 percent of the White cases and over 45 percent of White controls had an annual income of $25,000 or greater, compared with half those percentages among Black cases and controls, respectively. Annual income was based on the question 'For the past calendar year, what was your income before taxes (*i.e.*, money received by you and your spouse from wages, Social Security, welfare, other)?'

Race-adjusted and race-specific MM risks for 53 medical conditions/procedures are shown in Table 2. Except for a significant twofold risk of myeloma among Black men treated for urinary tract infection, no statistically significant associations were observed with any medical condition, overall or by race. An elevated risk, approaching statistical significance, was observed with drug allergies for both races combined (OR = 1.2), and for Blacks in particular (OR = 1.6). An evaluation of the specific drugs included in this

Table 1. Distribution of demographic variables for multiple myeloma by race

	Whites				Blacks			
	Cases (n = 367)		Controls (n = 1,164)		Cases (n = 206)		Controls (n = 967)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Age (yrs)								
30-39	3	(0.8)	27	(2.3)	9	(4.4)	26	(2.7)
40-49	19	(5.2)	150	(12.9)	22	(10.7)	101	(10.4)
50-59	74	(20.2)	332	(28.5)	41	(19.9)	242	(25.0)
60-69	136	(37.1)	344	(29.6)	79	(38.4)	309	(32.0)
70-79	134	(36.5)	304	(26.1)	52	(25.2)	283	(29.3)
80+	1	(0.3)	7	(0.6)	3	(1.5)	6	(0.6)
Mean age (yrs)		65.3		61.4		62.3		62.3
Standard deviation		(9.2)		(10.7)		(11.3)		(10.8)
Gender								
Male	193	(52.6)	742	(63.7)	91	(44.2)	614	(63.5)
Female	174	(47.4)	422	(36.3)	115	(55.8)	353	(36.5)
Education								
0-11 years	137	(37.3)	302	(25.9)	123	(59.7)	544	(56.3)
High school	116	(31.6)	370	(31.8)	52	(25.2)	247	(25.5)
College	112	(30.5)	483	(41.5)	31	(15.0)	176	(18.2)
Missing	2	(0.5)	9	(0.8)	0	—	0	—
Annual income*								
<$10,000	53	(14.4)	119	(10.2)	91	(44.2)	330	(34.1)
$10-$24,999	148	(40.3)	373	(32.0)	64	(31.1)	350	(36.2)
≥$25,000	122	(33.2)	556	(47.8)	34	(16.5)	220	(22.8)
Missing	44	(12.1)	116	(10.0)	17	(8.2)	67	(6.9)
Study site								
Atlanta (GA)	25	(6.8)	252	(21.6)	39	(18.9)	196	(20.3)
Detroit (MI)	167	(45.5)	443	(38.1)	89	(43.2)	420	(43.4)
New Jersey	175	(47.7)	469	(40.3)	78	(37.9)	351	(36.3)

* Based on question 'For the past calendar year, what was your income before taxes (*i.e.*, money received by you and your spouse from wages, Social Security, welfare, other)?'

category revealed that Black males had a statistically significant myeloma risk associated with allergies to penicillin (OR = 3.2; CI = 1.3-8.4). No significant associations with specific drugs were seen for Black females or Whites.

The ORs for MM according to the biologic and immunologic categories of medical conditions are shown in Table 3. For most biologic categories, there were no increased risks for Blacks or Whites either analyzed separately or combined. An elevated risk of 1.2, approaching statistical significance, was seen with the category of allergic conditions among Blacks. This slightly increased risk is not explained by the elevated MM risk seen for allergies to penicillin. Even though penicillin allergy contributes the most to the drug-allergy category for both Blacks (58.3 percent) and Whites (44.7 percent), penicillin allergy contributes less than 10 percent to all allergies for both race groups. An elevated, nonsignificant risk was observed for autoimmune disorders for Blacks. Whites did not show an association with MM and autoimmune disorders. There was no evidence of increasing myeloma risk with increasing level of exposure for any of the biologically related medical conditions. No statistically significant elevated risks for conditions categorized by immune response mechanism were observed for all races combined or for Blacks and Whites separately. Among Blacks, there was a suggestion of increased myeloma risk with increased exposure to conditions eliciting an anaphylactic response, however the test for linear trend was not significant ($P = 0.13$). A test for interaction using a continuous variable for anaphylactic conditions revealed significant differences by race ($P < 0.05$).

ORs associated with B-cell mediated conditions were nonsignificantly elevated for both races combined (OR = 1.9) and for Whites and Blacks separately (ORs = 1.7 and 2.2, respectively). However, no relation between number of B-cell mediated conditions and risk of myeloma was evident. A suggestion of a negative association with myeloma was observed with the category T-cell mediated conditions (similar

Table 2. Adjusted multiple myeloma odds ratios (OR) for selected medical conditions/procedures by race[a]

	Whites				Blacks				Total	
	Cases (n = 367)	Controls (n = 1,164)	OR[b]	(CI)[c]	Cases (n =206)	Controls (n = 967)	OR[b]	(CI)[c]	OR[d]	(CI)[c]
Allergies										
Allergy shots	18	89	0.7	(0.4-1.3)	8	37	0.9	(0.4-2.0)	0.8	(0.5-1.2)
Asthma	22	63	1.2	(0.7-2.1)	16	53	1.3	(0.7-2.3)	1.2	(0.8-1.8)
Drugs	53	161	1.1	(0.8-1.5)	19	52	1.6	(0.9-2.9)	1.2	(0.9-1.5)
Dust	13	61	0.8	(0.4-1.5)	9	34	1.2	(0.5-2.5)	0.9	(0.5-1.4)
Eczema	19	57	1.2	(0.7-2.0)	6	25	1.1	(0.4-2.7)	1.1	(0.7-1.8)
Hay fever	54	240	0.9	(0.7-1.3)	40	171	1.1	(0.7-1.6)	1.0	(0.8-1.3)
Household products	6	21	0.9	(0.3-2.4)	6	15	1.6	(0.6-4.3)	1.2	(0.6-2.3)
Severe allergic reaction	35	124	0.9	(0.6-1.4)	18	57	1.5	(0.9-2.6)	1.1	(0.8-1.5)
Autoimmune diseases										
Ankylosing spondylitis	0	2	—	—	0	0	—	—	—	—
Graves' disease	1	1	5.3	(0.2-114.0)	0	0	—	—	3.4	(0.2-61.1)
Hashimoto's disease	2	1	6.9	(0.5-88.6)	0	0	—	—	5.5	(0.5-64.4)
Idiopathic thromb. purpura	0	3	—	—	2	0	—	—	3.4	(0.6-21.5)
Pernicious anemia	6	19	0.8	(0.3-2.2)	5	12	1.5	(0.5-4.5)	1.1	(0.5-2.3)
Psoriasis	6	25	0.8	(0.3-2.0)	1	8	0.5	(0.1-4.2)	0.7	(0.3-1.7)
Rheumatoid arthritis	38	108	0.9	(0.6-1.4)	26	133	0.8	(0.5-1.3)	0.8	(0.6-1.1)
Scleroderma	0	2	—	—	0	0	—	—	—	—
Sjögren's disease	0	0	—	—	0	0	—	—	—	—
Sys. lupus erythematosus	1	0	—	—	1	2	2.1	(0.2-24.2)	4.1	(0.5-32.0)
Bacterial diseases										
Ear infection	22	104	0.7	(0.4-1.2)	2	22	0.4	(0.1-1.6)	0.7	(0.4-1.0)
Gonorrhea	7	21	1.6	(0.6-3.9)	19	116	1.0	(0.6-1.7)	1.0	(0.6-1.6)
Kidney disease	14	67	0.8	(0.4-1.4)	6	47	0.5	(0.2-1.3)	0.6	(0.4-1.1)
Osteomyelitis	3	5	1.7	(0.4-7.9)	3	6	2.3	(0.6-9.4)	2.0	(0.7-5.7)
Pancreatitis	2	10	1.0	(0.2-4.7)	0	8	—	—	0.5	(0.1-2.1)
Pneumonia	9	26	1.1	(0.5-2.4)	4	7	2.6	(0.7-9.2)	1.4	(0.7-2.7)
Rheumatic fever	15	31	1.4	(0.7-2.7)	7	39	0.7	(0.3-1.6)	1.1	(0.7-1.8)
Scarlet fever	36	113	0.9	(0.6-1.4)	6	28	1.0	(0.4-2.4)	0.9	(0.6-1.3)
Sinusitis	32	143	0.8	(0.5-1.2)	12	71	0.6	(0.3-1.2)	0.7	(0.5-1.0)
Strep throat	19	79	0.9	(0.5-1.5)	1	25	0.2	(0.0-1.3)	0.7	(0.4-1.2)
Syphilis	2	1	11.6	(0.8-173.0)	6	19	1.5	(0.6-4.0)	1.8	(0.8-4.3)
Tonsillitis	25	119	0.8	(0.5-1.2)	7	51	0.6	(0.3-1.3)	0.7	(0.5-1.0)
Tuberculosis	5	19	0.8	(0.3-2.2)	2	29	0.3	(0.1-1.3)	0.5	(0.2-1.2)
Urinary tract inf. (men)	37	148	1.0	(0.7-1.5)	15	57	2.0	(1.1-3.8)	1.2	(0.9-1.7)
Urinary tract inf. (women)	24	73	0.9	(0.5-1.5)	8	27	1.0	(0.4-2.3)	0.9	(0.6-1.4)
Vaccines										
Influenza	220	688	1.1	(0.8-1.4)	100	495	0.9	(0.7-1.2)	1.0	(0.8-1.2)
Polio	213	727	1.0	(0.8-1.4)	82	442	0.8	(0.6-1.1)	0.9	(0.7-1.1)
Smallpox	277	885	1.0	(0.7-1.4)	138	638	1.1	(0.7-1.5)	1.0	(0.8-1.3)
Tetanus	262	881	1.0	(0.8-1.4)	119	547	1.2	(0.8-1.7)	1.1	(0.8-1.4)
Viral diseases										
Chickenpox	235	812	0.8	(0.6-1.1)	131	633	0.9	(0.6-1.2)	0.8	(0.7-1.0)
Mononucleosis	6	26	1.2	(0.5-3.0)	0	0	—	—	1.0	(0.4-2.6)
Mumps	221	744	1.0	(0.8-1.3)	134	670	0.8	(0.6-1.2)	0.9	(0.7-1.1)
Polio	5	19	0.9	(0.3-2.5)	0	2	—	—	0.8	(0.3-2.2)

Continued . . .

Table 2. *Continued*

	Whites				Blacks				Total	
	Cases (n = 367)	Controls (n = 1,164)	OR[b]	(CI)[c]	Cases (n =206)	Controls (n = 967)	OR[b]	(CI)[c]	OR[d]	(CI)[c]
Miscellaneous conditions										
Blood transfusion	83	217	1.1	(0.8-1.5)	45	182	1.0	(0.7-1.5)	1.1	(0.9-1.4)
Chronic lung disease	21	75	0.8	(0.5-1.4)	8	38	1.0	(0.5-2.4)	0.9	(0.6-1.4)
Cirrhosis	2	8	0.8	(0.2-4.1)	1	14	0.3	(0.0-2.6)	0.5	(0.2-1.8)
Colitis	16	60	0.9	(0.5-1.5)	1	16	0.3	(0.1-2.1)	0.8	(0.5-1.3)
Diabetes	38	99	1.1	(0.7-1.7)	36	159	1.0	(0.6-1.4)	1.0	(0.8-1.4)
Goiter	1	5	0.9	(0.1-8.5)	2	2	3.2	(0.4-23.0)	1.5	(0.4-5.9)
Hepatitis	8	42	0.7	(0.3-1.6)	3	10	1.5	(0.4-5.4)	0.8	(0.4-1.6)
Hyperthyroidism	5	26	0.4	(0.2-1.1)	7	17	1.5	(0.6-3.7)	0.8	(0.4-1.5)
Hypothyroidism	18	51	1.1	(0.6-1.9)	2	15	0.5	(0.1-2.3)	0.9	(0.5-1.6)
Sarcoidosis	0	0	—	—	0	3	—	—	—	—
Shingles	39	113	1.0	(0.7-1.5)	11	31	1.7	(0.8-3.6)	1.2	(0.8-1.6)
Embedded shrapnel	16	72	0.8	(0.4-1.4)	3	40	0.4	(0.1-1.3)	0.6	(0.4-1.1)
Tonsillectomy	166	630	0.8	(0.6-1.0)	38	216	0.8	(0.5-1.1)	0.8	(0.6-0.9)

[a] Osteomyelitis diagnosed at least two years prior to multiple myeloma diagnosis: all other conditions diagnosed at least one year prior to multiple myeloma diagnosis.

[b] Odds ratios adjusted for age (≤64, ≥65), education (grades 0-11, high school or equivalent, college), study site (Atlanta, Detroit, New Jersey), and gender.

[c] CI = 95% confidence interval.

[d] Odds ratios adjusted for age (≤64, ≥65), education (grades 0-11, high school or equivalent, college), study site (Atlanta, Detroit, New Jersey), gender, and race.

Table 3. Adjusted multiple myeloma odds ratios (OR) by biologic and immunologic categories by race

	Whites				Blacks				Total	
	Cases (n = 349)	Controls (n = 1,092)	OR[a]	(CI)[b]	Cases (n =196)	Controls (n = 914)	OR[a]	(CI)[b]	OR[c]	(CI)[b]
Biologic category										
Childhood illness/vaccines										
Never	8	15	1.0	—	10	34	1.0	—	1.0	—
Ever	339	1,071	0.7	(0.3-1.8)	186	880	0.8	(0.4-1.6)	0.7	(0.4-1.3)
1-2	56	132	0.7	(0.3-1.8)	44	183	0.8	(0.4-1.9)	0.8	(0.4-1.5)
3-4	123	351	0.7	(0.3-1.8)	78	356	0.8	(0.4-1.6)	0.7	(0.4-1.3)
5+	160	588	0.7	(0.3-1.9)	64	341	0.7	(0.3-1.5)	0.7	(0.4-1.3)
Acute bacterial conditions										
Never	198	544	1.0	—	125	582	1.0	—	1.0	—
Ever	149	542	0.9	(0.7-1.1)	71	332	1.0	(0.7-1.4)	0.9	(0.8-1.4)
1-2	71	220	1.0	(0.7-1.3)	46	181	1.3	(0.9-1.9)	1.1	(0.8-1.4)
3-5	31	95	1.0	(0.6-1.6)	12	62	0.9	(0.5-1.7)	1.0	(0.7-1.4)
6+	47	227	0.7	(0.5-1.0)	13	89	0.6	(0.3-1.1)	0.6	(0.5-0.9)
Chronic bacterial conditions										
Never	337	1,055	1.0	—	191	873	1.0	—	1.0	—
Ever	10	31	1.1	(0.5-2.3)	5	41	0.6	(0.2-1.4)	0.8	(0.4-1.4)
Allergic conditions										
Never	194	570	1.0	—	121	622	1.0	—	1.0	—
Ever	153	516	1.1	(0.8-1.4)	75	292	1.2	(0.9-1.7)	1.1	(0.9-1.4)
1-2	135	419	1.1	(0.8-1.4)	66	259	1.2	(0.9-1.7)	1.2	(0.9-1.4)
3-4	11	57	0.8	(0.4-1.6)	6	24	1.1	(0.4-2.8)	0.9	(0.5-1.5)
5+	7	40	0.7	(0.3-1.6)	3	9	1.5	(0.4-5.9)	0.8	(0.4-1.6)
Autoimmune disease										
Never	322	1,037	1.0	—	187	892	1.0	—	1.0	—
Ever	15	49	1.0	(0.5-1.8)	9	22	1.7	(0.7-3.7)	1.2	(0.7-1.9)

Continued . . .

Table 3. *Continued*

	Whites				Blacks				Total	
	Cases (n = 349)	Controls (n = 1,092)	OR[a]	(CI)[b]	Cases (n =196)	Controls (n = 914)	OR[a]	(CI)[b]	OR[c]	(CI)[b]
Immunologic category										
Anaphylaxis										
Never	196	577	1.0	—	121	630	1.0	—	1.0	—
Ever	151	509	1.1	(0.8-1.4)	75	284	1.3	(0.9-1.8)	1.1	(0.9-1.4)
1-2	143	466	1.1	(0.8-1.4)	68	264	1.3	(0.9-1.8)	1.1	(0.9-1.4)
3+	8	43	0.8	(0.4-1.8)	7	20	1.5	(0.6-3.8)	1.0	(0.5-1.8)
Delayed hypersensitivity										
Never	44	85	1.0	—	21	79	1.0	—	1.0	—
Ever	303	1,001	0.8	(0.5-1.2)	175	835	0.8	(0.5-1.4)	0.8	(0.6-1.1)
1-2	277	870	0.8	(0.5-1.2)	166	772	0.9	(0.5-1.4)	0.8	(0.6-1.1)
3+	26	131	0.7	(0.4-1.2)	9	63	0.6	(0.3-1.5)	0.6	(0.4-1.0)
Neutralization										
Never	8	30	1.0	—	11	59	1.0	—	1.0	—
Ever	339	1,056	1.6	(0.7-3.6)	185	855	1.1	(0.6-2.2)	1.2	(0.7-2.1)
1-2	90	202	1.8	(0.8-4.1)	81	305	1.3	(0.7-2.7)	1.5	(0.9-2.5)
3-5	191	574	1.7	(0.7-3.9)	88	448	1.0	(0.5-2.0)	1.2	(0.7-2.1)
6+	56	280	1.1	(0.5-2.7)	16	102	0.7	(0.3-1.6)	0.8	(0.5-1.5)
Neutralization and other responses										
Never	315	1,001	1.0	—	188	862	1.0	—	1.0	—
Ever	32	85	1.1	(0.7-1.7)	8	52	0.6	(0.3-1.4)	1.0	(0.7-1.4)
Neutralization and cytotoxic										
Never	247	718	1.0	—	148	690	1.0	—	1.0	—
Ever	100	368	0.9	(0.7-1.2)	48	224	1.1	(0.8-1.6)	1.0	(0.8-1.2)
1-2	57	184	1.0	(0.7-1.4)	34	141	1.3	(0.9-2.1)	1.1	(0.8-1.4)
3+	43	184	0.8	(0.6-1.2)	14	83	0.8	(0.4-1.5)	0.8	(0.6-1.1)
Cell mediation										
B-cell mediation										
Never	5	22	1.0	—	4	12	1.0	—	1.0	—
Ever	342	1,064	1.7	(0.6-4.6)	192	872	2.2	(0.8-6.4)	1.9	(0.9-3.9)
1-2	66	149	1.8	(0.6-5.0)	62	240	2.6	(0.9-7.6)	2.1	(1.0-4.5)
3-5	161	443	1.9	(0.7-5.3)	87	422	2.1	(0.7-6.1)	1.9	(0.9-4.0)
6-9	56	183	1.6	(0.6-4.6)	25	106	2.4	(0.8-7.4)	1.9	(0.9-3.9)
10+	59	289	1.2	(0.4-3.4)	18	104	1.6	(0.5-5.2)	1.3	(0.6-2.8)
T-cell mediation										
Never	44	85	1.0	—	21	79	1.0	—	1.0	—
Ever	303	1,001	0.8	(0.5-1.2)	175	835	0.8	(0.5-1.4)	0.8	(0.6-1.1)
1-2	277	870	0.8	(0.5-1.2)	166	771	0.9	(0.5-1.4)	0.6	(0.6-1.1)
3+	26	131	0.7	(0.4-1.2)	9	64	0.6	(0.3-1.4)	0.6	(0.4-1.0)

[a] Odds ratios adjusted for gender, age (≤64, ≥65), education (0-11 grades, high school, college), study site (Atlanta, Detroit, New Jersey).
[b] CI = 95% confidence interval.
[c] Odds ratios adjusted for age (≤64, ≥65), education (grades 0-11, high school or equivalent, college), study site (Atlanta, Detroit, New Jersey), gender, and race.

to the delayed-hypersensitivity category), for both races.

To investigate possible CAS associations for a particular MM subtype, risks were determined for IgG and IgA subtypes for the combined races and then separately by race. IgG accounted for 38 percent of the MM cases for Whites and 52 percent for Blacks, followed by IgA (Whites, 19 percent; Blacks, 15 percent). Other subtypes included: IgM (0.8 percent) and IgD (0.8 percent) among Whites only; light chain myeloma (Whites, 7.9 percent; Blacks, 6.3 percent); and polyclonal MM (Whites, 1.9 percent; Blacks, 4.9 percent). Whites also had one case of IgE myeloma and one case of nonsecretory myeloma. For the remaining cases (Whites, 31 percent; Blacks, 23 percent), subtype was not available or not determined.

The odds ratios of IgG and IgA cases for selected medical conditions and biologic and immunologic categories are shown in Table 4. Individual medical conditions in this analysis were selected based on

Table 4. Adjusted odds ratios of IgG and IgA multiple myeloma for selected medical conditions, and biologic and immunologic groupings by race

	IgG myeloma								IgA myeloma								Total IgG		Total IgA	
	Whites				Blacks				Whites				Blacks							
	Cases (*n*=138)	Controls (*n*=1164)	OR[a]	(CI)[b]	Cases (*n*=106)	Controls (*n*=967)	OR[a]	(CI)[b]	Cases (*n*=70)	Controls (*n*=1164)	OR[a]	(CI)[b]	Cases (*n*=30)	Controls (*n*=967)	OR[a]	(CI)[b]	OR[c]	(CI)[b]	OR[c]	(CI)[b]
Medical condition																				
Drug allergies	26	161	1.5	(0.9-2.4)	9	52	1.5	(0.7-3.1)	9	161	1.0	(0.5-2.3)	3	52	1.5	(0.4-5.3)	1.4	(0.9-2.1)	1.1	(0.6-2.1)
Diabetes	14	99	1.1	(0.6-2.1)	22	159	1.2	(0.7-2.0)	11	99	1.6	(0.8-3.3)	6	159	1.1	(0.4-2.7)	1.2	(0.8-1.7)	1.4	(0.8-2.4)
Eczema	12	57	2.1	(1.1-4.2)	4	25	1.4	(0.5-4.1)	3	57	1.1	(0.3-3.5)	1	25	1.2	(0.2-9.4)	1.8	(1.0-3.1)	1.1	(0.4-3.1)
Gonorrhea	2	21	1.4	(0.3-6.4)	7	116	0.7	(0.3-1.6)	4	21	4.6	(1.4-15.2)	4	116	1.4	(0.4-4.4)	0.7	(0.4-1.5)	1.8	(0.8-4.1)
Kidney infection	3	67	0.5	(0.1-1.5)	2	47	0.4	(0.1-1.5)	6	67	2.0	(0.8-5.0)	0	47	—	—	0.4	(0.2-1.0)	1.2	(0.5-2.9)
Rheumatic fever	7	31	1.9	(0.8-4.5)	6	39	1.3	(0.5-3.1)	2	31	1.0	(0.2-4.4)	1	39	0.7	(0.1-5.1)	1.5	(0.8-2.8)	0.8	(0.3-2.8)
Shingles	6	113	1.4	(0.8-2.4)	7	31	2.2	(0.9-5.2)	6	113	0.8	(0.3-1.9)	0	31	—	—	1.6	(1.0-2.5)	0.7	(0.3-1.6)
Syphilis	0	1	—	—	4	19	2.0	(0.7-6.2)	1	1	∞	—	1	19	1.5	(0.2-12.3)	1.9	(0.6-5.6)	2.8	(0.6-12.6)
Embedded shrapnel	7	72	1.0	(0.4-2.2)	1	40	0.3	(0.0-1.9)	4	72	0.8	(0.3-2.4)	0	40	—	—	0.7	(0.3-1.4)	0.7	(0.2-1.8)
Tuberculosis	2	19	0.8	(0.2-3.7)	0	29	—	—	0	19	—	—	0	29	—	—	0.4	(0.1-1.5)	—	—
Urinary tract infection (men)	10	148	0.8	(0.4-1.6)	6	57	1.4	(0.6-3.5)	16	148	2.4	(1.2-4.7)	2	57	1.8	(0.4-8.9)	0.9	(0.5-1.7)	2.3	(1.2-4.2)
Biologic grouping																				
Childhood illness/ vaccines	129	1,071	1.1	(0.2-5.0)	99	880	1.3	(0.4-4.2)	65	1,071	0.6	(0.1-2.8)	27	880	0.5	(0.1-2.4)	1.2	(0.5-3.1)	0.6	(0.2-1.7)
Acute bacterial conditions	59	542	1.0	(0.7-1.5)	35	332	0.9	(0.6-1.4)	31	542	1.1	(0.6-1.8)	10	332	0.9	(0.4-2.1)	0.9	(0.7-1.2)	1.0	(0.7-1.5)
Allergic conditions	70	516	1.6	(1.1-2.3)	38	292	1.2	(0.8-1.8)	24	516	0.8	(0.5-1.4)	8	292	0.8	(0.3-1.8)	1.4	(1.0-1.8)	0.8	(0.5-1.3)
Autoimmune disease	8	49	1.6	(0.7-3.5)	5	22	1.8	(0.6-4.9)	2	49	0.8	(0.2-3.5)	1	22	1.3	(0.2-10.7)	1.6	(0.8-2.9)	0.9	(0.3-3.1)
Immunologic grouping																				
Anaphylaxis	69	509	1.6	(1.1-2.3)	38	284	1.2	(0.8-1.9)	24	509	0.8	(0.5-1.4)	8	284	0.8	(0.4-1.9)	1.4	(1.0-1.8)	0.8	(0.5-1.3)
Delayed hyper-sensitivity	114	1,001	0.8	(0.4-1.4)	91	835	0.8	(0.4-1.6)	55	1,001	0.6	(0.3-1.2)	25	835	0.7	(0.2-2.1)	0.8	(0.5-1.2)	0.6	(0.3-1.1)
Neutralization	128	1,056	1.7	(0.5-5.7)	96	855	1.0	(0.4-2.4)	65	1,056	1.2	(0.3-5.3)	29	855	∞	—	1.2	(0.6-2.4)	2.2	(0.5-9.4)
Neutralization and other responses	15	85	1.5	(0.8-2.7)	6	52	1.0	(0.4-2.3)	5	85	0.9	(0.3-2.3)	1	52	0.5	(0.1-3.7)	1.3	(0.8-2.1)	0.8	(0.3-1.8)
Neutralization and cytotoxic	36	369	0.9	(0.6-1.4)	24	224	1.1	(0.6-1.7)	25	368	1.5	(0.9-2.5)	7	224	1.2	(0.5-2.9)	0.9	(0.7-1.3)	1.3	(0.8-2.0)
Cell mediation																				
B-cell mediation	129	1,064	1.6	(0.4-7.0)	100	872	2.3	(0.5-9.6)	65	1,064	0.8	(0.2-3.4)	29	872	∞	—	1.9	(0.7-5.3)	1.5	(0.3-6.3)
T-cell mediation	114	1,001	0.8	(0.4-1.4)	91	835	0.8	(0.4-1.6)	55	1,001	0.6	(0.3-1.2)	25	835	0.7	(0.2-2.1)	0.8	(0.5-1.2)	0.6	(0.3-1.1)

[a] OR = odds ratios adjusted for gender, age (≤64, ≥65), education (grades 0-11, high school, college), study site (Atlanta, Detroit, New Jersey).
[b] CI = 95% confidence intervals.
[c] OR = odds ratios adjusted for age (≤64, ≥65), education (grades 0-11, high school or equivalent, college), study site (Atlanta, Detroit, New Jersey), gender, and race.
∞ = infinity.

previously reported associations[23] and associations observed with either IgA or IgG multiple myeloma in the present study. For both races combined, marginally elevated risks of IgG myeloma were observed for eczema, the biologic category of allergic conditions, and the immunologic category of anaphylaxis. An elevated IgG myeloma risk, approaching statistical significance, was seen for drug allergies. These patterns of increased risk of IgG also were observed for Whites and Blacks separately. For IgA myeloma, however, nonsignificant risks of 1.2 or less were seen for these conditions or categories regardless of race. A marginally significant, elevated risk of IgG myeloma, but not IgA myeloma, was associated with shingles due to the increased risk among Blacks, and for the immunologic category of anaphylaxis among Whites (nonsignificant increase for Blacks).

For both races combined, a significant association was evident for urinary tract infection among men for IgA myeloma but not for IgG myeloma. Although not consistent across races, nonsignificantly elevated risks were observed for both IgG and IgA myeloma in the combined analysis for the following medical conditions or categories: diabetes; syphilis; neutralization; and B-cell mediation. No association or a negative association was seen for both myeloma subtypes and each race for tuberculosis, delayed hypersensitivity, and T-cell mediation. A statistically significant, elevated risk of IgA myeloma was seen for gonorrhea among White men.

Discussion

This epidemiologic investigation of MM evaluates CAS using an approach that classifies medical conditions by their respective immunologic response. Since this study was designed specifically to examine differences in risk factors between Blacks and Whites, we were able to assess whether CAS is responsible for the higher incidence of MM among Blacks in the US.

In this evaluation of CAS, the risks for MM for both races combined were not elevated significantly for any of the 53 individual medical conditions/procedures that were evaluated. In the race-specific analysis, only the risk for urinary tract infection among Black men was significantly elevated. MM risks for certain individual medical-conditions including allergies and shingles were higher among Blacks than Whites. Although allergic conditions have been associated with MM in other studies,[12,13,18,21,22] the populations under investigation were primarily White and the specific allergies linked with MM risk differed among these studies.

Analyses by immunoglobulin type revealed a significant risk of IgG myeloma among Whites with eczema, and a significant risk of IgA myeloma among Whites with gonorrhea and White men with urinary tract infection. We know of only one previous case-control study[23] which attempted to evaluate the relationship between individual medical conditions and immunoglobulin type of MM. Contrary to those findings, we did not observe an association between IgA myeloma and tuberculosis or embedded shrapnel.

Since it did not appear that CAS could be evaluated appropriately based on individual medical conditions, a more biologically plausible approach was taken by categorizing the medical conditions according to their biologically and immunologically related responses. Using this approach, we hoped to identify the particular biologic or immunologic type of antigenic stimulation related to MM. The results of these analyses, however, revealed that myeloma risk was not associated significantly with any of these categories for both races combined or for Whites and Blacks separately. Significant associations were seen with IgG multiple myeloma among Whites with the biologic category of allergic conditions and the immunologic category of anaphylaxis, while no significant findings were observed for IgA myeloma.

Because MM is a malignancy of the B-lymphocyte, it has been hypothesized that immune responses to medical conditions that are mediated by B-cells, rather than T-cells, could evoke more 'stress' in the plasma cells.[27] This, in turn, could increase B-cell proliferation and thereby increase the risk for MM. Accordingly, we collapsed the immune response categories further into either B- or T-lymphocyte type of mediation. Although MM risk was increased for B-cell mediated conditions, with Blacks and Whites showing a similar pattern, none of the ORs were statistically significant. A suggestion of a negative association was observed with T-cell-mediated conditions for both races; however, it is unclear how to interpret these findings.

When evaluating these results, several issues need to be considered. It is possible that our lack of significant findings could be due to our inability to interview all eligible cases of MM. Medical history information was not ascertained on deceased cases and, thus, we cannot rule out the possibility that cases who died had a greater prevalence of the chronic diseases of interest than the cases who survived to be interviewed.

While recall bias may be of concern, cases or controls should not have been familiar with the CAS hypothesis or any *a priori* associations between myeloma and specific medical conditions. In an effort to decrease invalid responses, the questionnaire specifically asked about medical conditions that were diagnosed by a physician at least one year prior to the interview. Although medical utilization may have differed by race in our study,

especially for non-debilitating diseases (*e.g.*, ear infection, sinusitis), the identification of more serious disorders are less likely to have been affected. Since our analysis involved multiple comparisons, it is possible that some of the associations reported are due to chance.

Our evaluation of medical history data was based on interview only. It was not possible to verify both positive and negative responses to the conditions on the questionnaire, owing to the fact that lifetime exposures were of interest. Thus, there is the potential for non-differential misclassification. A review paper that attempted to evaluate agreement between questionnaire interview data and medical record data observed a high level of agreement for past history of diseases such as tuberculosis, hepatitis, and asthma (kappa values indicated moderate to good agreement).[28] For rarer diseases, agreement between recall and the medical record data tended to be higher for autoimmune conditions such as systemic lupus erythematosus. The review also revealed that true validation of medical conditions is difficult, given that a reference to a diagnosis can be made in the medical record without any available confirmed test result and that some conditions (*e.g.*, hay fever, sinusitis) are not recorded consistently in medical records. The potential for underestimates of the risk of MM due to nondifferential misclassification of certain medical conditions may exist in this study, however the extent to which the MM risk estimates may have been affected is unknown.

This study used questionnaire data to evaluate the CAS hypothesis by assessing risks for MM associated with individual medical conditions, grouped biologic and immunologic conditions, and B-cell and T-cell mediated conditions. Although a few positive associations were noted, results in general, did not support a causal relationship between CAS and MM. Any differences in risk between Blacks and Whites for individual or grouped conditions were minimal and would not explain the higher incidence of MM in Blacks compared with Whites in the US. However, medical history based on interview data may not be sufficient to evaluate CAS. Even when historical medical records (*i.e.*, from Health Maintenance Organizations) are used to ascertain medical histories of cases and controls, CAS does not appear to be a strong risk factor for MM.[21] Perhaps the relationship between B-cell stress in immune response and risk for MM could be examined better through the utilization of biologic markers or specific cytokines that are associated with B-cell activity. Until a biologic marker is developed that can measure lifetime immune stimulation, it is unlikely that the relationship between CAS and MM can be evaluated adequately by epidemiologic studies.

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Appendix. Categories of conditions classified by biologic, immunologic, and lymphocyte response

Categories of biologically-related conditions[a]

Childhood illnesses/vaccinations: chickenpox, infectious mononucleosis, influenza vaccination, mumps, and polio, smallpox and tetanus vaccinations.

Acute bacterial infections: ear infections, gonorrhea, kidney disease, rheumatic fever, pneumonia, scarlet fever, sinusitis, strep throat, syphilis, tonsillitis, urinary tract infections.

Chronic bacterial infections: osteomyelitis, pancreatitis, tuberculosis.

Allergic conditions: allergy shots, asthma, eczema, hay fever, non-food allergies, severe allergic reaction.

Autoimmune diseases: ankylosing spondylitis, Graves' disease, Hashimoto's disease, idiopathic thrombocytopenic purpura (ITP), pernicious anemia, psoriasis, scleroderma, Sjögren's disease, systemic lupus erythematosus.

Categories of immunologically-related conditions[b]

Anaphylaxis: asthma, eczema, hay fever, non-food allergies, severe allergic reaction.

Delayed hypersensitivity: cirrhosis of the liver, infectious mononucleosis, mumps, polio, smallpox vaccination, syphilis, tuberculosis.

Neutralization: allergy shots, chickenpox, diabetes, ear infections, Graves' disease, hyperthyroidism, hypothyroidism, influenza vaccination, kidney disease/pyelonephritis, pernicious anemia, polio vaccination, scarlet fever, shingles, sinusitis, tetanus vaccination.

Neutralization and other responses: colitis, Hashimoto's disease, rheumatic fever.

Neutralization and cytotoxicity: gonorrhea, osteomyelitis, pneumonia, strep throat, tonsillitis, urinary tract infection.

Immune complex: ankylosing spondylitis, scleroderma.

Immune complex and other responses: Sjögren's disease, systemic lupus erythematosus.

Categories of lymphocyte-mediated conditions[c]

B-cell mediation: neutralization,[d] immune complex,[d] anaphylaxis,[d] cytotoxicity,[d] rheumatic fever, systemic lupus erythematosus.

T-cell mediation: delayed hypersensitivity,[d] granuloma (sarcoidosis).

Mixed B- and T-cell mediation[e]: colitis, Hashimoto's disease, Sjögren's disease.

[a] Blood transfusion, colitis, hepatitis, cirrhosis of the liver, chronic lung disease, hyperthyroidism, hypothyroidism, diabetes, sarcoidosis, embedded shrapnel, shingles, goiter, tonsillectomy, and polio were excluded from this classification. Rheumatoid arthritis was omitted due to subjects' perceived confusion with other forms of arthritis.
[b] Goiter, hepatitis, chronic lung disease, pancreatitis, psoriasis, tonsillectomy, and blood transfusions were excluded from this categorization scheme.
[c] The same conditions were excluded from this classification as those previously listed in the Appendix.
[d] Refer to the immunologically related conditions listed above for the complete list of conditions.
[e] Colitis, Hashimoto's disease, and Sjögren's disease are all separate medical conditions that have both types of lymphocyte mediation.